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(54) Title: FLUORO AND SULPHONYLAMINO CONTAINING 3,6-DISUBSTITUTED AZABICYCLO (3.1.0) HEXANE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract: This invention generally relates to the derivatives of novel 3,6 disubstituted azabicyclo[3.1.0] hexane's. The compounds of this invention are MUSCARINIC receptor antagonists which are useful, inter-ail for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through MUSCARINIC receptors. The invention also relates to processes for the preparation of the compounds of the invention, pharmaceutical compositions containing the compounds of the present invention and the methods of treating the diseases mediated through MUSCARINIC receptors.

FLUORO AND SULPHONYLAMINO CONTAINING 3,6-DISUBSTITUTED AZABICYCLO (3.1.0) HEXANE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention generally relates to the derivatives of novel 3,6 disubstituted azabicyclo[3.1.0] hexanes.

The compounds of this invention are muscarinic receptor antagonists which are useful, inter-alia for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors.

The invention also relates to processes for the preparation of the compounds of the invention, pharmaceutical compositions containing the compounds of the present invention and the methods of treating the diseases mediated through muscarinic receptors.

BACKGROUND OF THE INVENTION

Muscarinic receptors as members of the G Protein Coupled Receptors (GPCRs) are composed of a family of 5 receptor sub-types (M_1, M_2, M_3, M_4 and M_5) and are activated by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor sub-types in the brain and other organs has been documented. For example, the M_1 subtype is located primarily in neuronal tissues such as cereberal cortex and autonomic ganglia, the M_2 subtype is present mainly in the heart where it mediates cholinergically induced bradycardia, and the M_3 subtype is located predominantly on smooth muscle and salivary glands (Nature, 1986; 323: 411; Science, 1987; 237: 527).

A review in Current opinions in Chemical Biology, 1999; 3: 426, as well as in Trends in Pharmacological Sciences, 2001; 22: 409 by Eglen et. al., describe the biological potentials of modulating muscarinic receptor subtypes by ligands in

different disease conditions like Alzheimer's disease, pain, urinary disease condition, chronic obstructive pulmonary disease etc.

A review in J. Med. Chem., 2000; 43: 4333 by Christian C. Felder et. al. describes therapeutic opportunities for muscarinic receptors in the central nervous system and elaborates on muscarinic receptor structure and function, pharmacology and their therapeutic uses.

The pharmacological and medical aspects of the muscarinic class of acetylcholine agonists and antagonists are presented in a review in Molecules, 2001, 6: 142.

N.J.M. Birdsall et. al. in Trends in Pharmacological Sciences, 2001; 22: 215 have also summarized the recent developments on the role of different muscarinic receptor subtypes using different muscaranic receptor of knock out mice.

Muscarinic agonists such as muscarine and pilocarpine and antagonists such as atropine have been known for over a century, but little progress has been made in the discovery of receptor subtype-selective compounds making it difficult to assign specific functions to the individual receptors. Although classical muscarinic antagonists such as atropine are potent bronchodilators, their clinical utility is limited due to high incidence of both peripheral and central adverse effects such as tachycardia, blurred vision, dryness of mouth, constipation, dementia, etc. Subsequent development of the quarterly derivatives of atropine such as ipratropium bromide are better tolerated than parenterally administered options but most of them are not ideal anti-cholinergic bronchodilators due to lack of selectivity for muscarinic receptor sub-types. The existing compounds offer limited therapeutic benefit due to their lack of selectivity resulting in dose limiting side-effects such as thirst, nausea, mydriasis and those associated with the heart such as tachycardia mediated by the M_2 receptor.

Annual review of Pharmacological Toxicol., 2001; 41: 691, describes the pharmacology of the lower urinary tract infections. Although anti muscarinic agents such as oxybutynin and tolterodine that act non-selectively on muscarinic receptors have been used for many years to treat bladder hyperactivity, the

clinical effectiveness of these agents has been limited due to the side effects such as dry mouth, blurred vision and constipation. Tolterodine is considered to be generally better tolerated than oxybutynin. (W.D.Steers et. al. in Curr. Opin. Invest. Drugs, 2: 268, C.R. Chapple et. al. in Urology, 55: 33), Steers WD, Barrot DM, Wein AJ, 1996, Voiding dysfunction: diagnosis classification and management. In Adult and Pediatric Urology, ed. JY Gillenwatter, JT Grayhack, SS Howards, JW Duckett, pp 1220-1325, St. Louis, MO; Mosby. 3rd edition.)

Despite these advances, there remains a need for development of new highly selective muscarinic antagonists which can interact with distinct subtypes, thus avoiding the occurrence of adverse effects.

Compounds having antagonistic activity against muscarinic receptors have been described in Japanese patent application Laid Open Number 92921/1994 and 135958/1994; WO 93/16048; U.S. Patent No. 3,176,019; GB 940,540; EP 0325 571; WO 98/29402; EP 0801067; EP 0388054; WO 9109013; U.S. Patent No. 5,281,601. U.S. Patent Nos. 6,174,900, 6,130,232 and 5,948,792; WO 97/45414 are related to 1,4-disubstituted piperidine derivatives; WO 98/05641 describes fluorinated, 1,4-disubstitued piperidine derivatives; WO 93/16018 and WO96/33973 are other close art references.

A report in J. Med. Chem., 2002; 44:984, describes cyclohexylmethyl piperidinyl triphenylpropioamide derivatives as selective M_3 antagonist discriminating against the other receptor subtypes.

SUMMARY OF THE INVENTION

The present invention provides novel fluoro and sulphonylamino containing 3,6-disubstituted azabicyclo[3.1.0]hexanes as muscarinic receptor antagonists which are useful as safe and effective therapeutic or prophylactic agents for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems and process for the synthesis of the novel compounds. Substitution on the cycloalkyl moeity improves both metabolic stability as well as subtype selectivity.

The invention also provides pharmaceutical compositions containing the novel compounds together with acceptable carriers, excipients or diluents which are useful for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems.

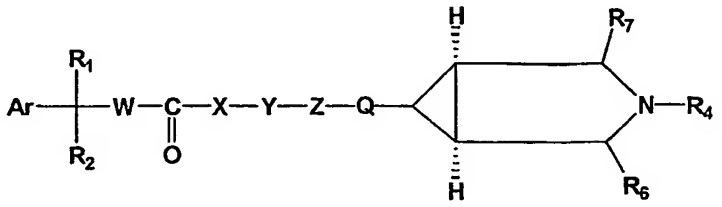
The present invention also includes within its scope prodrugs of the novel compounds. In general, such prodrugs will be functionalized derivatives of these compounds which readily get converted *in vivo* into the defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known to the artisan skilled in the art.

The invention also includes the enantiomers, diastereomers, N-oxides, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates of these compounds as well as metabolites having the same type of activity.

The invention further includes pharmaceutical compositions comprising the compounds of the present invention, their prodrugs, metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

Other advantages of the invention will be set forth in the description which follows, and in part will be apparent from the description or may be learnt by the practice of the invention. The objects and the advantages of the invention may be realized and obtained by means of the mechanisms and combinations pointed out in the appended claims.

In accordance with one aspect of the present invention, there is provided a compound having the structure of Formula I:



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), lower perhalo alkoxy (C_1-C_4), unsubstituted amino, N-lower alkyl (C_1-C_4) amino or N-lower alkyl (C_1-C_4) amino carbonyl;

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (e.g. fluorine, chlorine, bromine and iodine);

R_2 represents C_3-C_7 cycloalkyl ring in which from 1 to 4 hydrogen atoms are substituted with fluorine atoms, or sulphonamide derivatives;

W represents $(CH_2)_p$, where p represents 0 to 1;

X represents an oxygen, sulphur, nitrogen or no atom;

Y represents CHR_5CO wherein R_5 represents hydrogen or methyl or $(CH_2)q$ wherein q represents 0 to 4;

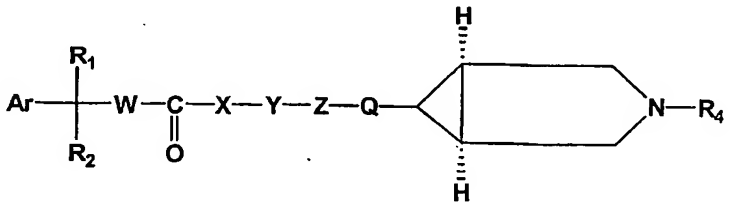
Z represents oxygen, sulphur or NR_{10}, wherein R_{10} represents hydrogen, C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl, alkoxy or CH_2CHR_9, wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);

R_6 and R_7 are independently selected from H, CH_3, COOH, $CONH_2$, NH_2, CH_2NH_2; and

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4), N-lower alkylamino carbonyl (C_1-C_4).

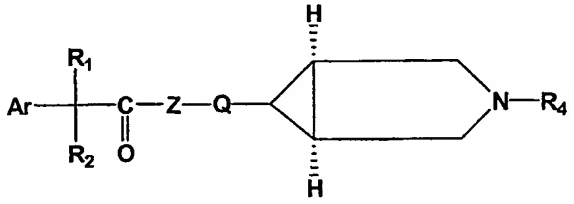
In accordance with a second aspect of the present invention, there is provided a compound having the structure of Formula II (Formula I, when R_6 and R_7 = H) and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R_1, R_2, W, X, Y, Z, Q, and R_4 are as defined for Formula I.



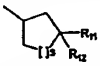
Formula II

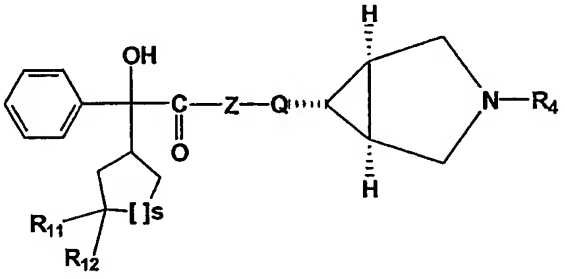
In accordance with a third aspect of the present invention there is provided a compound having the structure of Formula III (Formula I wherein W is $(CH_2)p$ where p = 0, X is no atom and Y is $(CH_2)q$ where q = 0, R_6 = H, R_7 = H) and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters,

enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R_1, R_2, Z, Q and R_4 are as defined for Formula I.



Formula III

In accordance with a fourth aspect of the present invention, there is provided a compound having the structure of Formula IV [Formula I when W is $(CH_2)p$ where p = 0, X is no atom and Y is $(CH_2)q$ where q=0, R_6 = H, R_7 = H, R_2 =  , where R_{11} is hydrogen or fluoro, R_{12} is fluoro or sulphonamide derivatives and s represents 1 to 2, R_1 is hydroxy, Ar is phenyl], and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein R_4, Z and Q are the same as defined for Formula I.



Formula IV

In accordance with a fifth aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors.

In accordance with a sixth aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or human suffering from a disease or disorder associated with muscarinic receptors, comprising

administering to a patient in need thereof, an effective amount of muscarinic receptor antagonist compound as described above.

In accordance with a seventh aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or human suffering from a disease or disorder of the urinary system which induce such urinary disorders as urinary incontinence, lower urinary tract symptoms (LUTS), etc.; respiratory system disorders such as bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, etc.; and gastrointestinal system disorders such as irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis with compounds as described above, wherein the disease or disorder is associated with muscarinic receptors.

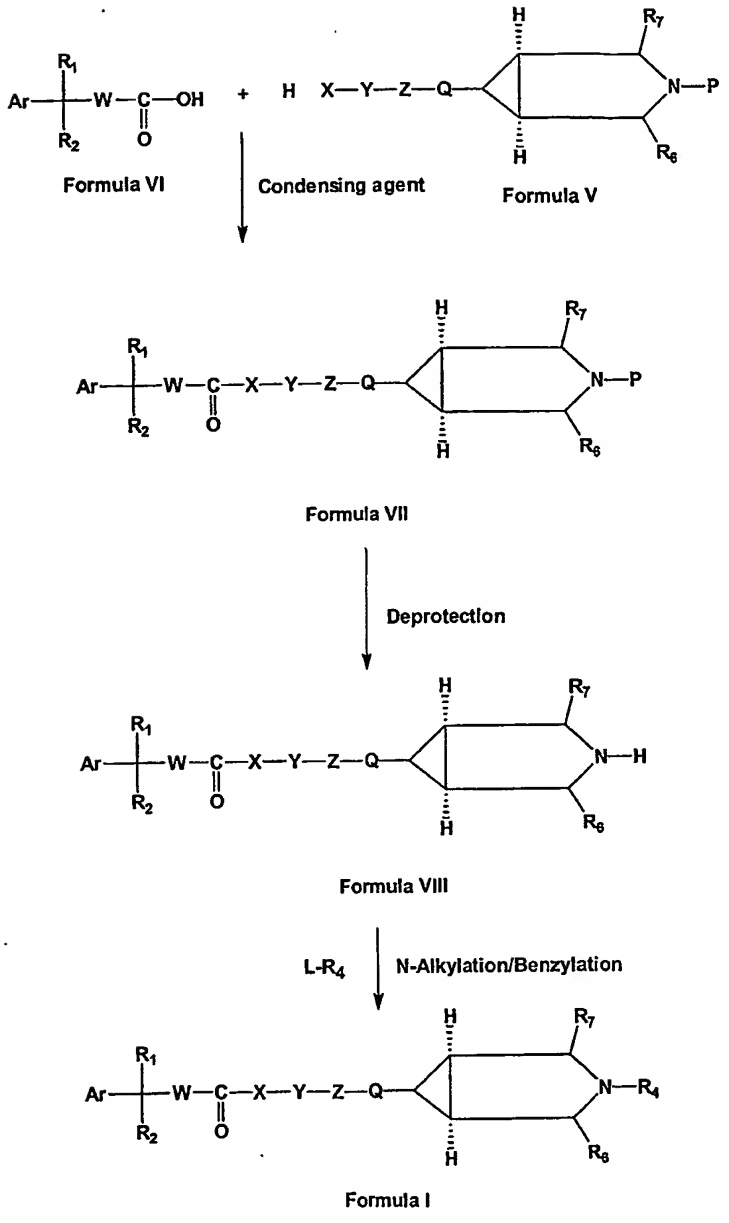
In accordance with the eighth aspect of the present invention, there are provided processes for preparing the compounds as described above.

The compounds of the present invention are novel and exhibit significant potency in terms of their activity, which was determined by *in vitro* receptor binding and functional assays and *in vivo* experiments using anaesthetized rabbit. The compounds that were found active in *in vitro* assay were tested *in vivo*. Some of the compounds of the present invention were found to be potent muscarinic receptor antagonists with high affinity towards M_3 receptors. Therefore, the present invention provides the pharmaceutical compositions for the possible treatment for the disease or disorders associated with muscarinic receptors. In addition, the compounds of the present invention can be administered orally or parenterally.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds of the present invention may be prepared by the following novel and inventive reaction sequences:

Scheme-I



The compounds of Formula I of the present invention may be prepared by the reaction sequence as shown in Scheme I. The preparation comprises condensing a compound of Formula V with the compound of Formula VI wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl

rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), lower perhalo alkoxy (C_1-C_4), unsubstituted amino, N-lower alkyl (C_1-C_4) amino or N-lower alkyl (C_1-C_4) amino carbonyl;

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (e.g. fluorine, chlorine, bromine and iodine);

R_2 represents a C_3-C_7 cycloalkyl ring in which from 1 to 4 hydrogen atoms are substituted with fluorine atoms, or sulphonamide derivatives;

W represents $(CH_2)_p$, where p represents 0 to 1;

X represents an oxygen, sulphur, nitrogen or no atom;

Y represents CHR_5CO wherein R_5 represents hydrogen or methyl or $(CH_2)q$ wherein q represents 0 to 4;

Z represents oxygen, sulphur or NR_{10}, wherein R_{10} represents hydrogen, C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl, alkoxy or CH_2CHR_9, wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);

R_6 and R_7 are independently selected from H, CH_3, COOH, $CONH_2$, NH_2, CH_2NH_2; and

P is any protecting group for an amino group, in the presence of a condensing agent to give a protected compound of Formula VII which on deprotection in the presence of a deprotecting agent in an organic solvent gives an unprotected intermediate of Formula VIII which is finally N-alkylated or benzylated with a suitable alkylating or benzylating agent, L-R_4 to give a compound of Formula I wherein L is any leaving group and R_4 represents C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from

halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4), N-lower alkylamino carbonyl (C_1-C_4).

P is any protecting group for an amino group for a compound of Formula V and is selected from benzyl and t-butyloxy carbonyl groups.

The reaction of the compound of Formula V with a compound of Formula VI to give a compound of Formula VII is carried out in the presence of a condensing agent which is selected from the group consisting of 1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU).

The reaction of the compound of Formula V with a compound of Formula VI to give a compound of Formula VII is carried out in a suitable solvent selected from the group consisting of N,N-dimethylformamide, dimethylsulfoxide, toluene, and xylene at a temperature ranging from about 0-140°C.

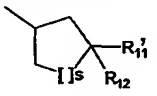
The deprotection of the compound of Formula VII to give a compound of Formula VIII is carried out with a deprotecting agent which is selected from the group consisting of palladium on carbon, trifluoroacetic acid (TFA) and hydrochloric acid.

The deprotection of the compound of Formula VII to give a compound of Formula VIII is carried out in a suitable organic solvent selected from the group consisting of methanol, ethanol, tetrahydrofuran and acetonitrile at temperatures ranging from about 10-50°C.

The N-alkylation or benzylation of the compound of Formula VIII to give a compound of Formula I is carried out with a suitable alkylating or benzylating agent, L-R_4 wherein L is any leaving group known in the art, preferably selected from halogen, O-mestyl and O-tosyl group.

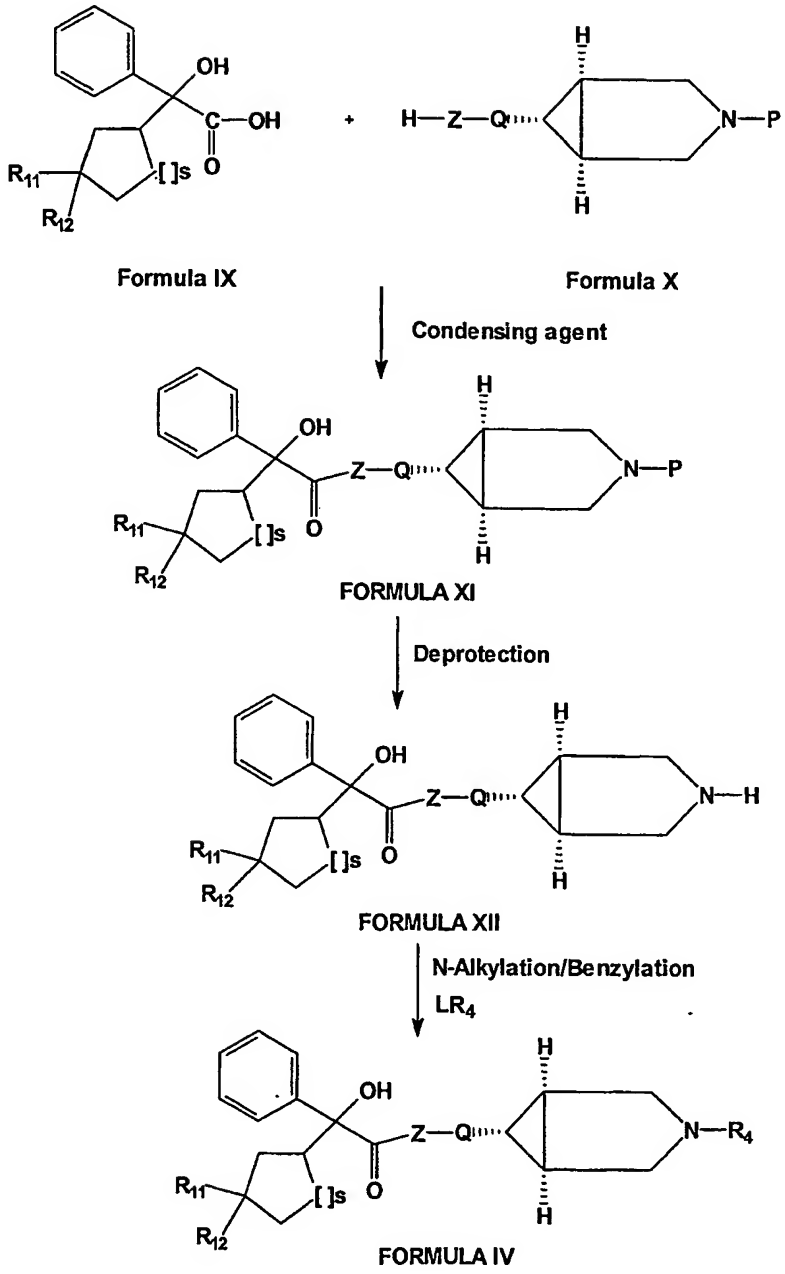
The N-alkylation or benzylation of the compound of Formula VIII to give a compound of Formula I is carried out in a suitable organic solvent such as N,N-dimethylformamide dimethylsulfoxide, tetrahydrofuran and acetonitrlie, at temperatures ranging from about 25-100°C.

Suitable salts of the compounds represented by the Formula I were prepared so as to solubilize the compound in aqueous medium for biological evaluations. Examples of such salts include pharmacologically acceptable salts such as inorganic acid salts (e.g. hydrochloride, hydrobromide, sulphate, nitrate and phosphorate), organic acid salts (e.g. acetate, tartrate, citrate, fumarate, maleate, toluenesulphonate and methanesulphonate). When carboxyl group is included in the Formula I as a substituent, it may be an alkali metal salt (e.g. sodium, potassium, calcium, magnesium, and the like). These salts may be prepared by the usual prior art techniques, such as treating the compound with an equivalent amount of inorganic or organic, acid or base in a suitable solvent.

The compound of Formula IV [Formula I, when W is $(CH_2)p$ where p=0, X is no atom, Y is $(CH_2)p$ where q=0, R_6=H, R_7=H, R_2=  where R_{11}=H or F, R_{12}=F and s represents 1 to 2,

R_1=OH, Ar=phenyl] may be prepared by the following reaction sequence as depicted in Scheme-II

Scheme-II



The preparation comprises condensing a compound of Formula IX with the compound of Formula X wherein Z, Q and s have the same meanings as defined earlier for Formula I, R_{11} is hydrogen or fluoro and R_{12} is fluoro. P is any protecting group for an amino group, in the presence of a condensing agent to

give a protected compound of Formula XI which on deprotection in the presence of a deprotecting agent in an organic solvent gives an unprotected intermediate of Formula XII which is finally N-alkylated or benzylated with a suitable alkylating or benzylating agent L-R_4 to give a compound of Formula IV wherein L is any leaving group and R_4 is defined above.

P is any protecting group for an amino group for a compound of Formula X and is selected from benzyl and t-butyloxy carbonyl groups.

The reaction of the compound of Formula IX with a compound of Formula X to give a compound of Formula XI is carried out in the presence of a condensing agent which is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU).

The reaction of the compound of Formula IX with a compound of Formula X to give a compound of Formula XI is carried out in a suitable solvent selected from the group consisting of N,N-dimethylformamide, dimethylsulphoxide, toluene, and xylene at a temperature ranging from about 0-140°C.

The deprotection of the compound of Formula XI to give a compound of Formula XII is carried out in a suitable organic solvent selected from the group consisting of methanol, ethanol, tetrahydrofuran and acetonitrile at temperatures ranging from about 10-50°C.

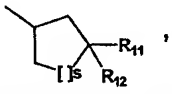
The deprotection of the compound of Formula XI to give a compound of Formula XII is carried out with a deprotecting agent which is selected from the group consisting of palladium on carbon, trifluoroacetic acid (TFA) and hydrochloric acid.

The N-alkylation or benzylation of the compound of Formula XII to give a compound of Formula IV is carried out with a suitable alkylating or benzylating agent, L-R_4 wherein L is any leaving group known in the art, preferably selected from halogen, O-mestyl and O-tosyl group.

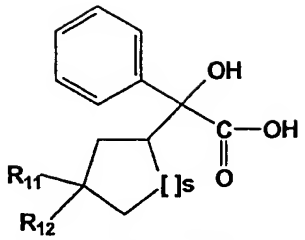
The N-alkylation or benzylation of the compound of Formula XII to give a compound of Formula IV is carried out in a suitable organic solvent such as N,N-dimethylformamide, dimethylsulphoxide, tetrahydrofuran and acetonitrile, at temperatures ranging from about 10-100°C.

Suitable salts of the compounds represented by the Formula IV were prepared so as to solubilize the compound in aqueous medium for biological evaluations. Examples of such salts include pharmacologically acceptable salts such as inorganic acid salts (e.g. hydrochloride, hydrobromide, sulphate, nitrate and phosphorate), organic acid salts (e.g. acetate, tartrate, citrate, fumarate, maleate, toluenesulphonate and methanesulphonate). When carboxyl group is included in the Formula I as a substituent, it may be an alkali metal salt (e.g. sodium, potassium, calcium, magnesium, and the like). These salts may be prepared by the usual prior art techniques, such as treating the compound with an equivalent amount of inorganic or organic, acid or base in a suitable solvent.

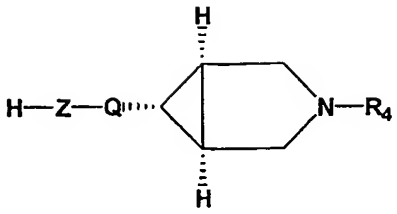
Acid of Formula IX can be synthesized following the procedures described in J.Org. Chem., 2001; 66:6775; Bioorg. and Med. Chem. 2000; 8:825 and references cited therein.

The compound of Formula IV [Formula I, when W is $(CH_2)p$ where p=0, X is no atom, Y is $(CH_2)p$ where q=0, R_6=R_7=H, R_2=  , where R_{11}=H or F, R_{12}=F or sulphonamide and s represents 1 to 2, R_1=OH, Ar=phenyl) can also be prepared by reaction sequence as shown in Scheme-III.

Scheme-III

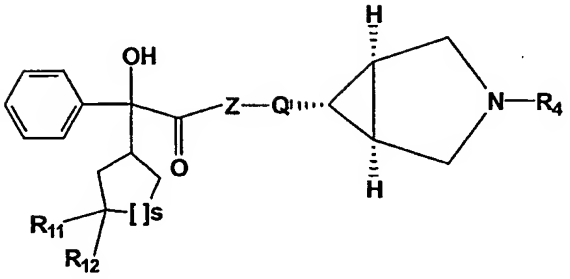


FORMULA IX



FORMULA XIII

Condensing agent



FORMULA IV

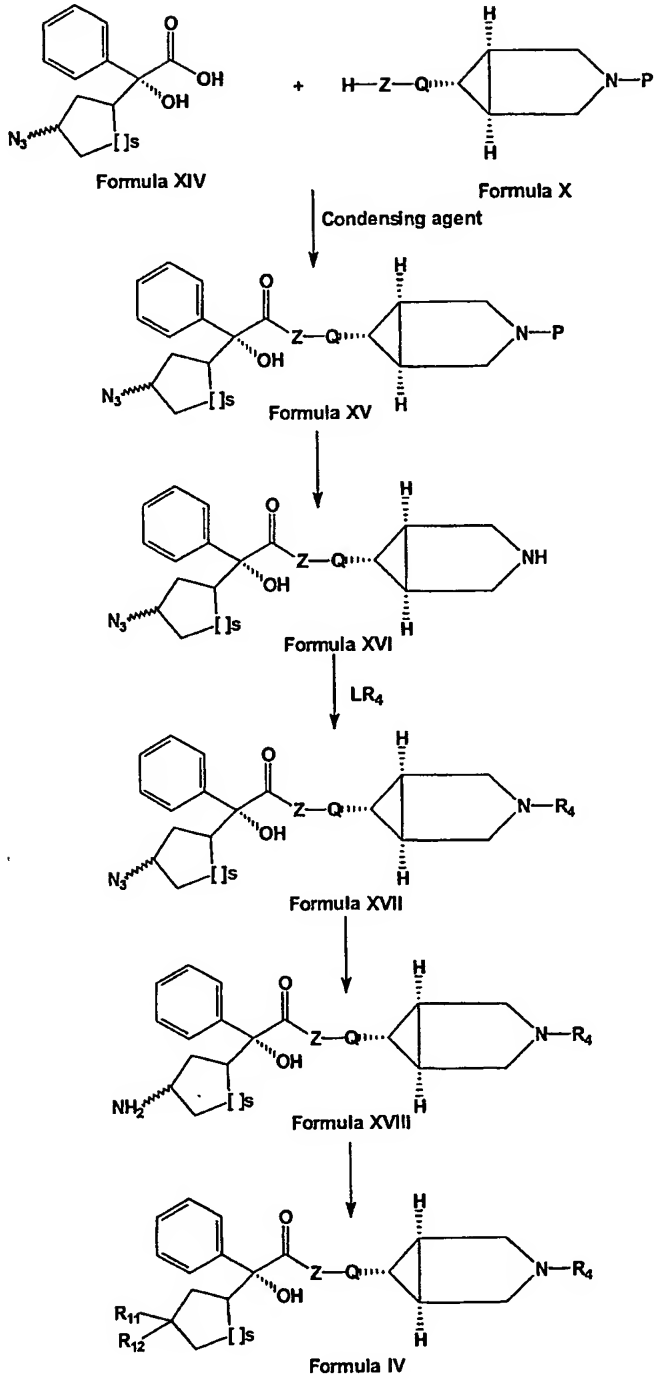
The preparation comprises condensing a compound of Formula IX with a compound of Formula XIII wherein Z, Q and R_4 have the same meanings as described earlier for Formula I.

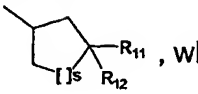
The reaction of the compound of Formula IX with a compound of Formula XIII is carried out in the presence of a condensing agent which is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU).

The reaction of the compound of Formula IX with a compound of Formula XIII is carried out in a suitable solvent selected from the group consisting of N,N-

dimethylformamide, dimethyl sulfoxide, toluene, and xylene at a temperature ranging from about 0-140°C.

Scheme-IV



The compound of Formula IV (Formula I, when W is $(CH_2)p$ where p=0, X is no atom, Y is $(CH_2)p$ where q=0, R_6=R_7=H, R_2=  , where R_{11}=H, R_{12}=substituted sulphonamide and s represents 1 to 2, R_1=OH, Ar=phenyl) of the present invention may be prepared by the reaction sequence as shown in Scheme-IV. The preparation comprises condensing a compound of Formula XIV with a compound of Formula X, where Z and Q have the same meanings as described earlier for Formula I to give a compound of Formula XV. The starting compound of Formula XIV was prepared by the known procedure described in Bioorganic and Medicinal Chemistry, 2000; 8:825.

The compound of Formula XVI is obtained by the deprotection of Formula XV in an organic solvent in the presence of a deprotecting agent. The intermediate of Formula XVI is finally N-alkylated or benzylated with suitable alkylating or benzylating agent L-R_4 to give a compound of Formula XVII wherein L is any leaving group and R_4 is the same as defined above.

P is any protecting group for an amino group for a compound of Formula X and is selected from benzyl and t-butyloxy carbonyl groups.

The reaction of the compound of Formula XIV with a compound of Formula X to give a compound of Formula XV is carried out in the presence of a condensing agent which is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU).

The reaction of the compound of Formula XIV with a compound of Formula X to give a compound of Formula XV is carried out in a suitable solvent selected from the group consisting of N,N-dimethylformamide, dimethylsulphoxide, toluene, and xylene at a temperature ranging from about 0°-140°C.

The deprotection of the compound of Formula XV to give a compound of Formula XVI is carried out in a suitable solvent selected from the group

consisting of methanol, ethanol, tetrahydrofuran and acetonitrile at temperature ranging from about 10°-50°C.

The N-alkylation or benzylation of the compound of Formula XVI to give a compound of Formula XVII is carried out with a suitable alkylating or benzylating agent, L-R_4 where L is any leaving group, known in the art, preferably selected from halogen, O-mestyl and O-tosyl group.

The N-alkylation or benzylation of the compound of Formula XVI to give a compound of Formula XVII is carried out in a suitable organic solvent such as N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and acetonitrile, at a temperature ranging from about 10°-100°C.

The reduction of the compound of Formula XVII to give a compound of Formula XVIII is carried out with triphenylphosphine in the presence of a suitable organic solvent such as tetrahydrofuran and water.

The compound XVIII on treatment with acid chlorides in a suitable solvent selected from the group consisting of dichloromethane, dichloroethane and chloroform gives the compound of Formula IV.

The acid chlorides may be selected from the group consisting of phenylacetylchloride, 4-nitrophenyl sulfonyl chloride, benzene sulfonyl chloride, benzyloxyacetyl chloride, 4-methoxy phenylsulfonyl chloride and 4-bromophenylsulfonyl chloride.

Suitable salts of the compounds represented by the Formula IV were prepared so as to solubilize the compound in aqueous medium for biological evaluations. Examples of such salts include pharmacologically acceptable salts such as inorganic acid salts (e.g. hydrochloride, hydrobromide, sulphate, nitrate and phosphorate), organic acid salts(e.g. acetate, tartrate, citrate, fumarate, maleate, toluenesulphonate and methanesulphonate). When carboxyl group is included in the Formula I as a substituent, it may be an alkali metal salt (e.g. sodium, potassium, calcium, magnesium, and the like). These salts may be prepared by the usual prior art techniques, such as treating the compound with an equivalent amount of inorganic or organic, acid or base in a suitable solvent.

In the above schemes, where specific bases, condensing agents, protecting groups, deprotecting agents, N-alkylating benzylating agents, solvents etc. mentioned, it is to be understood that other bases, condensing agents, protecting groups, deprotecting agents, N-alkylating, benzylating agents, solvents etc. known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

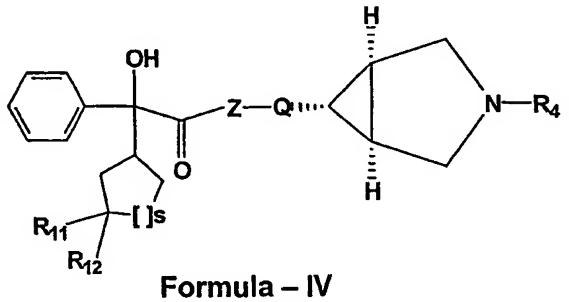
Preferred compounds according to the invention and capable of being produced by Scheme I-IV and are shown in Table 1 include:

Compound No.	Chemical Name
1A.	(2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenylacetamide
1B.	(2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenylacetamide
2.	(2R(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2- hydroxy-2-phenylacetamide
3.	(2Ror 2S)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenyl acetamide
4.	(2R or 2S)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenyl acetamide
5.	(2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-phenyl acetylamino cyclopentyl]-2- hydroxy-2-phenylacetamide
6.	(2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-(4-nitrophenyl)sulphonylamino cyclopentyl]-2-hydroxy-2-phenylacetamide
7.	(2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-phenylsulphonylamino cyclopentyl]-2-hydroxy-2-phenylacetamide
8.	(2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-benzyloxyacetylamino cyclopentyl]-2-hydroxy-2-phenylacetamide

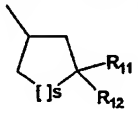
9. (2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-(4-methoxyphenyl) sulphonylamino cyclopentyl]-2-hydroxy-2-phenylacetamide

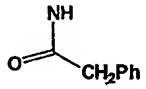
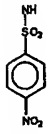
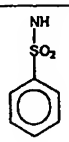
10. (2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-(4-bromophenyl)sulphonylamino cyclopentyl]-2-hydroxy-2-phenylacetamide

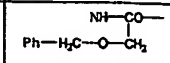
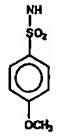
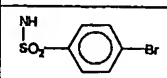
Table-I



Formula – IV

(Formula I, W is $(CH_2)p$ where p=0, X is no atom, Y is $(CH_2)q$ where q=0, R_6=R_7=H, R_2=  , s=1, R_1=OH, Ar=phenyl)

S.No.	R_{11}	R_{12}	Z	Q	R_4
1A	F	F	NH	CH_2	CH_2Ph
1B	F	F	NH	CH_2	CH_2Ph
2	H	F	NH	CH_2	CH_2Ph
3	F	F	NH	CH_2	CH_2Ph
4	H	F	NH	CH_2	CH_2Ph
5	H		NH	CH_2	CH_2Ph
6	H		NH	CH_2	CH_2Ph
7	H		NH	CH_2	CH_2Ph

S.No.	R_{11}	R_{12}	Z	Q	R_4
8	H		NH	CH_2	CH_2Ph
9	H		NH	CH_2	CH_2Ph
10	H		NH	CH_2	CH_2Ph

Because of their valuable pharmacological properties, the compounds of the present invention may be adminisered to an animal for treatment orally, or by parenteral route. The pharmaceutical compositions of the present invention are preferably produced and administered in dosage units, each unit containing a certain amount of at least one compound of the invention and/or at least one physiologically acceptable addition salt thereof. The dosage may be varied over extremely wide limits as the compounds are effective at low dosage levels and relatively free of toxicity. The compounds may be administered in the low micromolar concentration, which is therapeutically effective, and the dosage may be increased as desired up to the maximum dosage tolerated by the patient.

The present invention also includes within its scope prodrugs of the compounds of Formula I, II, III and IV. In general, such prodrugs will be functional derivatives of these compounds, which readily are converted *in vivo* into the defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known.

The present invention also includes the enantiomers, diastereomers, N-oxides, polymorphs, solvates and pharmaceutically acceptable salts of these compounds as well as metabolites having the same type of activity. The present invention further includes the pharmaceutical composition comprising the molecules of Formulae I, II, III and IV or prodrugs, metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with pharmaceutically acceptable carrier and optionally included excipient.

The examples mentioned below demonstrate the general synthetic procedure as well as the specific preparation of the preferred compound. The examples are provided to illustrate the details of the invention and should not be constrained to limit the scope of the present invention.

EXPERIMENTAL DETAILS

Various solvents, such as acetone, methanol, pyridine, ether, tetrahydrofuran, hexane, and dichloromethane, were dried using various drying agents according to the procedure described in the literature. IR spectrum were recorded as nujol mulls or a thin neat film on a Perkin Elmer Paragon Instrument and Nuclear Magnetic Resonance (NMR) were recorded on a Varian XL-300 MHz instrument using tetramethylsilane as an internal standard.

EXAMPLE 1

Preparation of (2R)- (1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenylacetamide (Compound Nos. 1A and 1B)

Step a: Preparation of (2R,5R)-2-tert-butyl-5-phenyl-1,3-dioxalan-4-one

The compound was synthesized following the procedure described in J.Org.Chem.2000;65:6283.

Step b: Preparation of (2R,5R)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxalan-4-one

To a suspension of the compound obtained at step a (1.36mmol) in tetrahydrofuran (12ml) was added lithium diisopropyl amide (LDA) in tetrahydrofuran (1.5 mmol) drop wise at –78°C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 2 hours. A solution of 2-cyclopenten-1-one (1.52mmol) in tetrahydrofuran (2ml) was added to the reaction mixture dropwise and stirred for additional 3hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried and the residue obtained after removing the solvents in vacuo was purified by column chromatography (100-200mesh silica gel). The product was eluted with 10% ethylacetate–hexane mixture.

^{1}HNMR($CDCl_3$) δ-values: 7.70-7.26 (m,5Ar-H), 5.43-5.37 (d,1H), 2.91-2.88 (m,1H), 2.37-1.77 (m,6H), 0.92 (s, 9H)

IR(DCM): 1791 and 1746 cm^{-1}

Step c: Preparation of (2R, 5R)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxalan-4-one

To a solution of the compound of step-b (1mmol) in chloroform (15ml) was added diethyl amino sulphur trifluoride (DAST), (3.3 mmol) at 0°C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 30 minutes and then at room temperature for 3 days. After being cooled to 0°C, the reaction mixture (RM) was quenched carefully by adding water. The organic layer was separated and the aqueous layer extracted with chloroform. The combined organic layers were dried and the residue obtained after removing the solvent was purified by column chromatography (100-200 mesh size silica gel) eluting the compound with 5% ethylacetate-hexane mixture.

^{1}HNMR($CDCl_3$) δ-values : 7.73-7.35 (m,5Ar-H), 5.49 (s,1H), 2.86-2.82 (m,1H), 2.27-1.80 (m,6H), 0.98 (s,H)

IR(DCM): 1793 cm^{-1}

Step d: Preparation of (2R)- [(1S or 1R)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenylaceticacid

The solution of the compound of step-c (1mmol) in methanol (10ml) was stirred with 3N aqueous sodium hydroxide solution for overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with dichloromethane. The aqueous layer was acidified with conc. hydrochloric acid and extracted with ethylacetate. The organic layer was dried and concentrated under reduced pressure to give the product.

m.pt. :123°C

^{1}HNMR($CDCl_3$) δ-values : 7.69-7.37(m,5Ar-H) , 3.29-3.20(m,1H) , 2.39-1.68 (m,6H)

Step e: Preparation of (1*α*,5*α*,6*α*)-6-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane.

The compound was synthesized as per the procedure of EP0413455A2.

Step f: Preparation of (2R)- (1α,5α,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenylacetamide.

A solution of (2R)-[(1S or 1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid (1mmol) and (1α,5α,6α)-6-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane(1.1mmol) in DMF (10ml) was cooled to 0°C. 1-Hydroxybenzotriazole (HOBT,1.1mmol) and N-methylmorpholine (NMM,2mmol) were added to the reaction mixture and reaction mixture stirred for 1hour at 0°C. 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC.HCl) (1mmol) was added to the reaction mixture at 0°C. The reaction mixture was stirred at 0°C for 1hour 30 minutes and then at room temperature for overnight. The reaction mixture was poured into saturated sodium bicarbonate solution and extracted with ethylacetate. The organic layer was washed with water and dried. The residue obtained after the removal of solvent was purified by column chromatography (100-200 mesh silica gel) eluting the compounds with 25-30% ethylacetate-hexane mixture.

Compound-1A:

^{1}HNMR ($CDCl_3$) δ-values: 7.58-7.22 (m, 10ArH), 6.33 (bs, 1H), 3.56 (s, 2H), 3.30 (m, 1H), 3.05-2.89 (m, 4H), 2.32-2.29 (m, 2H), 2.16-1.21 (m, 9H)

IR (KBr): 1654cm^{-1}

Compound-1B:

^{1}HNMR ($CDCl_3$) δ-values: 7.58-7.22 (m, 10ArH), 6.39 (bs, 1H), 3.56 (s, 2H), 3.48 (m, 1H), 3.48 (m, 1H), 3.07-2.89 (m, 4H), 2.32-2.29 (m, 2H), 2.16-1.21 (m, 9H)

IR (KBr): 1652cm^{-1}

Compound 1A and Compound 1B are a pair of diastereomers.

EXAMPLE 2

Preparation of (2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenyl acetamide (Compound No.2)

Step-a: Preparation of (2R)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-hydroxy cyclopentyl]-5-phenyl-1,3-dioxalan-4-one.

To a solution of (2R, 5R)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxalan-4-one (1 mmol) in methanol (10 ml) cooled to 0°C, sodium borohydride (2 mmol) was added in small lots with stirring. The reaction mixture was stirred at 0°C for 1 hr. It was concentrated under reduced pressure and the residue diluted with water and extracted with ethylacetate. The organic layer was dried and the residue obtained after the removal of solvents was purified by column chromatography (100-200 mesh silica gel) eluting the compound with 20% ethylacetate-hexane mixture.

^{1}HNMR($CDCl_3$) δ-values : 7.68-7.29 (m, 5H, ArH) , 5.45 (d,1H) , 4.30 (m, 1H), 3.25 (m, 1H), 2.65-2.63 (m, 1H), 1.80-1.63 (m, 6H), 0.92 (s, 9H)

IR(DCM): 1789 cm^{-1}, 3386 cm^{-1}

Step-b: Preparation of (2R)-2-tert-butyl-5-[1R or 1S, 3R or 3S]-3-fluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

The solution of the compound of step-a (1 mmol) in chloroform (10 ml) was cooled to 0°C and DAST (1.5 mmol) was added dropwise under nitrogen atmosphere. The reaction mixture (RM) was stirred at 0°C for 30 minutes and then at room temperature for 3 days. The RM was cooled and carefully quenched with aqueous ammonium chloride solution. The organic layer was separated and aqueous layer extracted with ethylacetate. The combined organic layer was dried and residue obtained after removing the solvents was purified by column chromatography (100-200 mesh, silica gel) eluting the compound with 5% ethylacetate-hexane mixture.

^{1}HNMR($CDCl_3$) δ-values : 7.68-7.28 (m, 5H, Ar-H) , 5.46 (d,1H), 5.39 (m, 1H), 2.90 (m, 1H), 1.98-1.25 (m, 6H), 0.93 (s, 9H)

Step-c: Preparation of (2R)-[(1R or 1S, 3R or 3S]-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

The compound was synthesized following the procedure of Example 1, step-d using (2R, 5R)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one instead of (2R, 5R)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

^{1}HNMR($CDCl_3$) δ-values: 7.66-7.27 (m, 5Ar-H), 5.30-5.00 (m, H), 3.32-3.16 (m, 1H), 2.05-1.26 (m, 6H).

IR(DCM): 1710 cm^{-1}

Step-d: Preparation of (2R)-(1*α*, 5*α*, 6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[1R or 1S, 3R or 3S]-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide.

The compound was synthesized following the procedure of Example 1, step-f, using (2R)- [(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenyl acetic acid instead of (2R)-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

^{1}HNMR($CDCl_3$) δ-values: 7.71-7.24 (m, 10H, Ar-H), 6.04 (b, 1H), 5.21-5.10 (m, 1H), 3.55 (s, 2H), 3.26-2.86 (m, 5H), 2.31-2.28 (m, 2H), 2.00-1.20 (m, 9H).

EXAMPLE 3

Preparation of (2R or 2S)-(1*α*,5*α* ,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenyl acetamide (Compound No.3)

Step a: Preparation of (2R or 2S,5R or 5S)-2-tert-butyl-5-phenyl-1,3-dioxalan-4-one

The compound was synthesized as per the procedure described in J.Org.Chem. 2000;65:6283, using DL-Mandelic acid instead of R-(-)-Mandelic acid.

Step b: Preparation of (2R or 2S,5R or 5S)-2-tert-butyl-5-[(1R or1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxalan-4-one

The compound was synthesized following the procedure of Example1,step-b,using (2R or 2S, 5R or 5S)-2-tert-butyl-5-phenyl-1,3-dioxalan-4-one instead of (2R,5R)-2-tert-butyl-5-phenyl-1,3-dioxalan-4-one.

Step c: Preparation of (2R or 2S, 5R or 5S)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxalan-4-one

The compound was prepared following the procedure of Example1,step-c, using(2R or 2S, 5R or 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxalan-4-one instead of (2R,5R)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxalan-4-one.

^{1}HNMR($CDCl_3$) δ-values : 7.67-7.29(m,5Ar-H) , 5.34(s,1H) , 2.80-2.76(m,1H), 2.23-1.70(m,6H) , 0.92(s,9H)

Step d: Preparation of (2Ror 2S,5R or 5S)-2- [(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

The compound was synthesized following the procedure of Example1,step-d –d, using (2R or 2S, 5R or 5S)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxalan-4-one instead of (2R,5R)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxalan-4-one.

^{1}HNMR($CDCl_3$) δ- values : 7.65-7.31(m,5Ar-H) , 3.23-3.14(m,1H) , 2.25-1.62(m, 6H)

IR (KBr): 1724 cm^{-1}

Step e: Preparation of (2R or 2S)- (1*α*,5 *α* ,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenyl acetamide

The compound was synthesized following the procedure of Example 1,step-f, using (2R or 2S, 5R or 5S)-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid instead of (2R,5R)-2 -[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

^{1}HNMR($CDCl_3$) δ-values: 7.58-7.23 (m,10Ar-H), 6.33 (bs,1H), 3.56 (s,2H), 3.47 (s,1H), 3.33-3.25(m,1H) , 3.05-2.88(m,4H), 2.31-2.28(m, 2H) ,2.21-1.66(m,9H)

IR (KBr) : 1652 cm^{-1}

HPLC: Single compound (Diastereomers could not be separated).

EXAMPLE 4

Preparation of (2Ror 2S)-(1α,5α ,6α)-N-[3-benzyl-3-azablcyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2- hydroxy-2-phenyl acetamide (Compound No.4)

Step a: Preparation of (2R or 2S, 5R or 5S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-hydroxycyclopentyl]-5-phenyl-1,3-dioxalan-4-one

To a solution of (2R or 2S, 5R or 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (1mmol) in methanol (10ml)cooled to 0°C. Sodium borohydride (2mmol) was added in small lots with stirring. The RM was stirred at 0°C for 1 hour. It was concentrated under reduced pressure and the residue diluted with water and extracted with EtOAc. The organic layer was dried and the residue obtained after removal of solvents was purified by column chromatography (100-200mesh silicagel) eluting the compound with 20%EtOAc-hexane mixture.

^{1}HNMR($CDCl_3$) δ-values : 7.68-7.29(m,5Ar-H) , 5.45(d,1H), 4.3(m,1H), -3.25(m,1H), 2.65-2.63(m,1H), 1.80-1.63(m,6H), 0.92(s,9H)

IR (DCM) : 1789 cm^{-1}, 3386cm^{-1}

Step b: Preparation of (2R or 2S, 5R or 5S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-5-phenyl-1,3-dioxalan-4-one

A solution of the compound of step-a (1mmol) in chloroform (10ml) was cooled to 0°C and DAST (1.5mmol) was added dropwise under nitrogen atmosphere. The RM was stirred at 0°C for 30 minutes and then at room temperature for 3 days. The RM was cooled and quenched with aqueous ammonium chloride solution. The organic layer was separated and aqueous layer extracted with EtOAc. The combined organic layers were dried and the residue obtained after removing the solvents was purified by column chromatography (100-200 mesh size, silica gel) eluting the compound with 5% EtOAc-hexane mixture.

^{1}HNMR($CDCl_3$) δ-values : 7.69-7.23(m,5Ar-H) , 5.42(d,1H), 5.28-5.16(m,1H), 2.92-2.86(m,1H), 1.97-1.24(m,6H), 0.90(s,9H)

IR (DCM) : 1791cm^{-1}

Step c: Preparation of (2R or 2S)-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenyl acetic acid

The compound was synthesized following the procedure of Example1, step-d, using (2R or 2S, 5R or 5S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-5-phenyl-1,3-dioxalan-4-one instead of (2R,5R)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxalan-4-one

^{1}HNMR($CDCl_3$) δ-values : 7.66-7.25(m,5Ar-H) , 5.30-4.99(m,1H), 3.81-3.76(m,1H), 2.01-1.64(m,6H)

IR (KBr) : 1722cm^{-1}

Step d: Preparation of (2R or 2S)- (1*α*,5*α*,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2- hydroxy-2-phenyl acetamide.

The compound was synthesized following the procedure of Example1, step-f, using (2R or 2S)-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenyl acetic acid instead of (2R)-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

^{1}HNMR($CDCl_3$) δ-values : 7.66-7.25(m,10Ar-H) ,6.05(bs,1H), 5.30-5.03 (m,1H),3.98 (s,2H), 3.56-2.87 (m,5H), 2.31-2.28(m,2H),1.97-1.11(m,9H)

IR (DCM) : 1652cm^{-1}

EXAMPLE 5

Preparation of (2R)-(1*α*,5*α*,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-phenylacetylamino cyclopentyl]-2- hydroxy-2-phenylacetamide (Compound No.5)

Step a: Preparation of (2R, 5R)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-azidocyclopentyl]-5-phenyl-1,3-dioxalan-4-one

To a solution of (2R, 5R)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-hydroxycyclopentyl]-5-phenyl-1,3-dioxalan-4-one(1mmol) and triethylamine (2.5 mmol) in ethyl acetate (10ml) was added methane sulphonyl chloride (2mmol) and the RM stirred for 1 hour at 0°C and then at room temperature for 1hour. Saturated aq. sodium bicarbonate solution was added, the organic layer separated and washed with water .The organic layer was dried and the residue obtained after the removal of solvent was used as such for the next step.

The residue (1mmol) was dissolved in DMF (10ml) and to it sodium azide (4mmol) was added. The RM was heated at 90-95°C for 4 hours, cooled to room

temperature, diluted with water and extracted with EtOAc. The organic layer was dried and the residue obtained after removing the solvent was used as such.

^{1}HNMR($CDCl_3$) δ-values : 7.66-7.26 (m,5Ar-H), 5.40 (s,1H), 4.00-3.97 (m,1H), 2.83-2.78 (m,1H), 1.80-1.04 (m,6H), 0.93 (s,9H)

IR (DCM) : 1791 and 2099cm^{-1}

Step b: Preparation of (2R)-[(1Ror 1S, 3R or 3S)-3-azidocyclopentyl]-2-hydroxy-2-phenyl acetic acid

To a solution of the compound of step-a (1mmol) in 10ml of methanol, 3N aq. sodium hydroxide solution was added and the RM stirred for overnight at room temperature. The RM was concentrated under reduced pressure, diluted with water and extracted with dichloromethane. The aqueous layer was acidified with 1N hydrochloric acid and extracted with chloroform. The organic layer was washed with water, dried and concentrated under reduced pressure to give the required product.

^{1}HNMR($CDCl_3$) δ-values : 7.65-7.26(m,5Ar-H) , 4.07-3.97 (m,1H), 3.22-3.14 (m,1H), 1.89-1.25 (m,6H)

IR (DCM) : 1712 and 2102cm^{-1}

Step c: Preparation of (2R)- (1α, 5α, 6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-azidocyclopentyl]-2- hydroxy-2-phenylacetamide

To a solution of the compound of step-b (1mmol) and (1α, 5α, 6α)-6-aminomethyl-3-benzyl-3-azabicyclo[3.1.0] hexane (0.9mmol) in DMF(10ml) was added NMM (2mmol) and HOBT (1.1mmol) at 0°C and stirred at the same temperature for 1hour. EDC.HCl (1mmol) was then added and the RM stirred for 1 hour at 0°C and then at room temperature for 4 days. The RM was poured into water and extracted with EtOAc. The organic layer was dried and the residue obtained after the removal of solvent was purified by column chromatography.

^{1}HNMR($CDCl_3$) δ-values : 7.74-7.22 (m,10Ar-H), 6.07 (bs,1H), 3.98-3.96 (m,1H), 3.55 (s,2H), 3.04-2.99 (m,5H), 2.31-2.28 (m,2H), 1.76-1.19 (m,9H)

IR (DCM) : 1654 and 2097cm^{-1}

Step-d: Preparation of (2R)-(1α, 5α, 6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-aminocyclopentyl]-2- hydroxy-2-phenyl acetamide

To a solution of the compound of, step-c, (9mmol) in a mixture of THF and water (75+15ml), triphenyl phosphine (27mmol) was added and the RM refluxed for 18 hours. The RM was cooled to room temperature, solvent removed in vacuo and the residue diluted with water. The pH was made acidic with 1N HCl and the RM extracted with chloroform. The aqueous layer was then made basic with 1N sodium hydroxide solution and extracted with chloroform. The organic layer was washed with water, dried and concentrated under reduced pressure. The residue was used as such for the next step.

Step e: Preparation of (2R)-(1α, 5α, 6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-phenylacetylamino cyclopentyl]-2-hydroxy-2-phenylacetamide

To a solution of the compound of step-d, triethylamine (2.2mmol), dimethyl aminopyridine (1mg) in chloroform was added phenylacetyl chloride (2.2mmol) at 0°C. The RM was stirred for overnight at room temperature. Aqueous sodium hydroxide was added and the organic layer separated. The organic layer was washed with water, dried and the solvent removed in vacuo. The residue was purified by column chromatography.

m.pt.:56-61°C

IR (DCM) : 1650 cm^{-1}

EXAMPLE 6

Preparation of (2R)-(1α,5α,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-(4-nitrophenyl)sulphonylamino-cyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No.6)

The compound was synthesized following the procedure of Example 5, step-e, using 4-nitrophenyl sulphonyl chloride instead of phenylacetyl chloride.

m.pt.:67-71°C

^{1}HNMR($CDCl_3$) δ-values: 8.35-8.26 (m, 2ArH), 8.06-7.97 (m,2ArH), 7.51-7.26 (m,10ArH), 6.34 (bs,1H), 3.67-2.90 (m,9H), 2.35-1.15 (m,10H)

IR (KBr) : 1652 and 1529 cm^{-1}

EXAMPLE 7

Preparation of (2R)- (1α, 5α, 6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-phenylsulphonylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No.7)

The compound was synthesized following the procedure of Example 5, step-e, using benzene sulphonyl chloride instead of phenylacetyl chloride.

m.pt.:52-56°C

^{1}HNMR($CDCl_3$) δ-values: 7.88-7.26 (m, 15ArH), 6.26 (bs,1H), 3.67-2.86(m,9H), 2.35-1.10(m,12H)

IR (KBr) : 1654 cm^{-1}

EXAMPLE 8

Preparation of (2R)- (1α,5α,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-benzyloxyacetylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No. 8)

The compound was synthesized following the procedure of Example 5, step-e, using benzyloxyacetyl chloride instead of phenylacetyl chloride.

^{1}HNMR($CDCl_3$) δ-values: 7.59-7.26 (m, 15ArH), 6.26 (bs,1H), 4.55 (d,2H), 3.95-3.56 (m,4H), 3.28 (s,2H), 3.04-2.90 (m,4H), 2.32-2.29 (m,2H), 2.05-1.13 (m,10H)

IR (DCM) : 1655 cm^{-1}

EXAMPLE 9

Preparation of (2R)-(1α, α,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(amino methyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-(4-methoxyphenyl)sulphonylamino cyclo pentyl]-2-hydroxy-2-phenylacetamide (Compound No. 9)

The compound was synthesized following the procedure of Example 5, step-e, using 4-methoxyphenyl sulphonyl chloride instead of phenylacetyl chloride.

^{1}HNMR($CDCl_3$) δ-values: 7.85-6.96(m, 14ArH), 6.30(bs,1H),3.89(s,3H), 3.6 (s,2H), 3.05-2.91 (m,5H), 2.36-2.34 (m,2H), 1.83-0.93 (m,10H)

IR (DCM) : 1661 cm^{-1}

EXAMPLE 10

Preparation of (2R)-(1α,5α,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(amino methyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-(4-bromophenyl)sulphonylaminocyclo-pentyl]-2- hydroxy-2-phenylacetamide (Compound No. 10)

The compound was synthesized following the procedure of Example 5, step-e, using 4-bromophenyl sulphonyl chloride instead of phenylacetyl chloride.

^{1}HNMR($CDCl_3$) δ-values: 7.73-7.26 (m,14ArH), 6.26 (bs,1H), 3.57-2.86 (m,7H), 2.33-2.29(m,2H), 1.85-1.19(m,10H)

IR (DCM) : 1651 cm^{-1}

Biological Activity

Radioligand Binding Assays:

The affinity of test compounds for M_2 and M_3 muscarinic receptor subtypes was determined by [^{3}H]-N-methylscopolamine binding studies using rat heart and submandibular gland respectively as described by Moriya et al., (Life Sci, 1999,64(25):2351-2358) with minor modifications.

Membrane preparation: Submandibular glands and heart were isolated and placed in ice cold homogenising buffer (HEPES 20mM, 10mM EDTA, pH 7.4) immediately after sacrifice. The tissues were homogenised in 10 volumes of homogenising buffer and the homogenate was filtered through two layers of wet gauze and filtrate was centrifuged at 500g for 10min. The supernatant was subsequently centrifuged at 40,000g for 20 min. The pellet thus obtained was resuspended in same volume of assay buffer (HEPES 20 mM, EDTA 5mM, pH 7.4) and were stored at -70^{o}C until the time of assay.

Ligand binding assay: The compounds were dissolved and diluted in DMSO. The membrane homogenates (150-250 µg protein) were incubated in 250 µl of assay buffer (HEPES 20 mM, pH 7.4) at 24-25^{o}C for 3h. Non-specific binding was determined in the presence of 1 µM atropine . The incubation was terminated by vacuum filtration over GF/B fiber filters(Wallac). The filters were then washed with ice cold 50mM Tris HCl buffer (pH 7.4). The filter mats were

dried and bound radioactivity retained on filters was counted. The IC_{50} & Kd were estimated by using the non-linear curve fitting program using G Pad Prism software. The value of inhibition constant Ki was calculated from competitive binding studies by using Cheng & Prusoff equation *(Biochem Pharmacol, 1973,22: 3099-3108)*, $Ki = IC_{50} /(1+L/Kd)$, where L is the concentration of $[^3H]$NMS used in the particular experiment.

Functional Experiments using Isolated rat bladder:

Methodology:

Animals were euthanized by overdose of urethane and whole bladder was isolated and removed rapidly and placed in ice cold Tyrode buffer with the following composition (mMol/L) NaCl 137; KCl 2.7; $CaCl_2$ 1.8; $MgCl_2$ 0.1; $NaHCO_3$ 11.9; NaH_2PO_4 0.4; Glucose 5.55 and continuously gassed with 95% O_2 and 5 % CO_2.

The bladder was cut into longitudinal strips (3mm wide and 5-6 mm long) and mounted in 10 ml organ baths at 30° C, with one end connected to the base of the tissue holder and the other end connected to a polygraph through a force displacement transducer. Each tissue was maintained at a constant basal tension of 2 g and allowed to equilibrate for 1 hour during which the PSS was changed every 15 min. At the end of equilibration period the stabilization of the tissue contractile response was assessed with 1µmol/L of Carbachol consecutively for 2-3 times. Subsequently a cumulative concentration response curve to carbachol (10^{-9} mol/L to 3 X 10^{-5} mol/L) was obtained. After several washes, once the baseline was achieved, cumulative concentration response curve was obtained in presence of NCE (NCE added 20 min. prior to the second CRC).

The contractile results were expressed as % of control E max. ED50 values were calculated by fitting a non-linear regression curve (Graph Pad Prism). pKB values were calculated by the formula pKB = - log [(molar concentration of antagonist/ (dose ratio-1))]

where,

dose ratio = ED50 in the presence of antagonist/ED50 in the absence of antagonist.

The result of the in-vitro test are listed in Table II.

In –Vitro tests

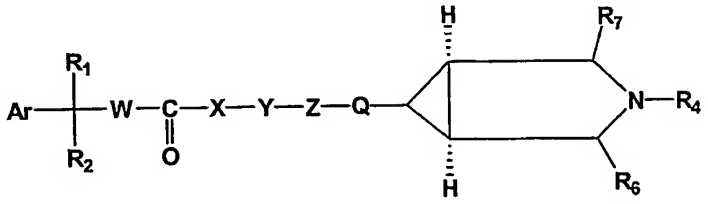
Table-II

	Receptor Binding Assay		Functional Assay pK_B
	M_2 pKi	M_3 pKi	
Compound No. 1A	6.87	8.25	9.1±0.2
Compound No. 1B	6.64	8.21	8.98±0.06
Compound No. 2	6.9	8.4	8.84±0.07
Compound No. 3	6.6	8.2	8.55±0.25
Compound No. 4	6.86	8.23	8.33±0.15
Compound No. 5	6.08	7.4	7.07±0.11
Compound No. 6	<5.8	7.66	7.21±0.20
Compound No. 7	<5.8	7.3	6.89±0.29
Compound No. 8	6.68	7.46	7.08±0.18
Compound No. 9	<6	6.69	-
Compound No. 10	<6	6.89	-

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

1. A compound having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), lower perhalo alkoxy (C_1-C_4), unsubstituted amino, N-lower alkyl (C_1-C_4) amino or N-lower alkyl (C_1-C_4) amino carbonyl;

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (fluorine, chlorine, bromine or iodine);

R_2 represents a C_3-C_7 cycloalkyl ring in which from 1 to 4 hydrogen atoms are substituted with fluorine atoms, or sulphonamide derivatives;

W represents $(CH_2)_p$, where p represents 0 or 1;

X represents oxygen, sulphur, nitrogen or no atom;

Y represents CHR_5CO wherein R_5 represents hydrogen or methyl or $(CH_2)q$ wherein q represents 0 to 4;

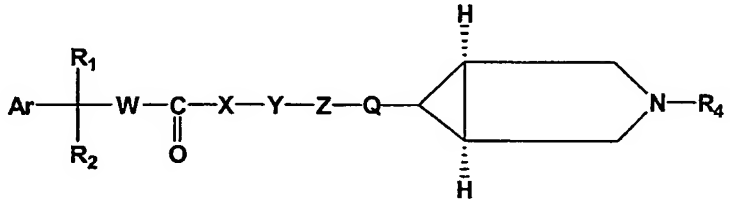
Z represents oxygen, sulphur or NR_{10}, wherein R_{10} represents hydrogen or C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);

R_6 and R_7 are independently selected from H, CH_3, COOH, $CONH_2$, NH_2 or CH_2NH_2; and

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4).

2. A compound having the structure of Formula II



Formula II

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three

substituents independently selected from lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), lower perhalo alkoxy (C_1-C_4), unsubstituted amino, N-lower alkyl (C_1-C_4) amino or N-lower alkyl (C_1-C_4) amino carbonyl;

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (fluorine, chlorine, bromine or iodine);

R_2 represents a C_3-C_7 cycloalkyl ring in which from 1 to 4 hydrogen atoms are substituted with fluorine atoms, or sulphonamide derivatives;

W represents $(CH_2)_p$, where p represents 0 or 1;

X represents oxygen, sulphur, nitrogen or no atom;

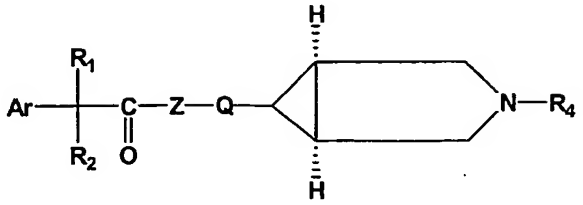
Y represents CHR_5CO wherein R_5 represents hydrogen or methyl or $(CH_2)q$ wherein q represents 0 to 4;

Z represents oxygen, sulphur or NR_{10}, wherein R_{10} represents hydrogen or C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4); and

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4).

3. A compound having the structure of Formula III



Formula III

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, distereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), lower perhalo alkoxy (C_1-C_4), unsubstituted amino, N-lower alkyl (C_1-C_4) amino or N-lower alkyl (C_1-C_4) amino carbonyl;

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (fluorine, chlorine, bromine or iodine);

R_2 represents a C_3-C_7 cycloalkyl ring in which from 1 to 4 hydrogen atoms are substituted with fluorine atoms, or sulphonamide derivatives;

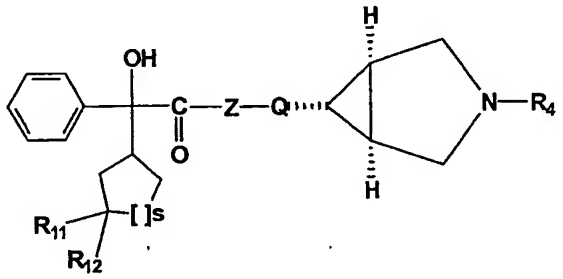
Z represents oxygen, sulphur or NR_{10}, wherein R_{10} represents hydrogen or $C_{1\text{-}6}$ alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, $C_{1\text{-}6}$, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4); and

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl,

heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4).

4. A compound having the structure of Formula IV



Formula IV

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, N-oxides, prodrugs or metabolites, wherein R_{11} is hydrogen or fluoro, R_{12} is fluoro or sulphonamide derivatives and s represents 1 to 2;

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-

C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4);

Z represents oxygen, sulphur or NR_{10}, wherein R_{10} represents hydrogen or C_{1-6} alkyl; and

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4).

5. A compound selected from the group consisting of:

(2R)- (1*α*,5*α* ,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenylacetamide (Compound No.1A)

(2R)-(1*α*,5*α* ,6*α*)- N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenylacetamide (Compound No.1B)

(2R)-(1*α*,5*α* ,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2- hydroxy-2-phenylacetamide (Compound No.2)

(2Ror 2S)-(1*α*,5*α* ,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2- hydroxy-2-phenylacetamide (Compound No.3)

(2R or 2S)-(1*α*,5*α* ,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No.4)

(2R)-(1*α*,5*α* ,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-phenylacetylamino cyclopentyl]-2- hydroxy-2-phenylacetamide (Compound No. 5)

(2R)-(1*α*,5*α* ,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-(4-nitrophenyl) sulphonylaminocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No.6)

(2R)-(1*α*,5*α* ,6*α*)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1Ror 1S, 3R or 3S)-3-phenylsulphonylamino cyclopentyl]-2- hydroxy-2-phenylacetamide (Compound No.7)

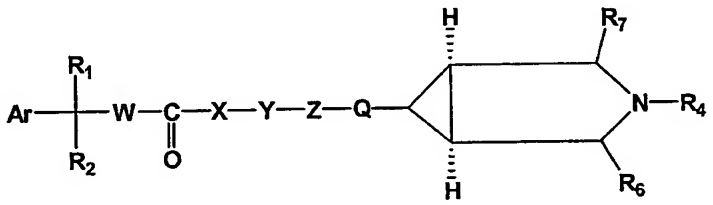
(2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-benzyloxyacetylaminocyclopentyl]-2- hydroxy-2-phenylacetamide (Compound No.8)

(2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-(4-methoxyphenyl) sulphonylaminocyclo pentyl]-2-hydroxy-2-phenylacetamide (Compound No.9)

(2R)-(1α,5α ,6α)-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl]-2-[(1R or 1S, 3R or 3S)-3-(4-bromophenyl)sulphonylamino cyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No.10)

6. A pharmaceutical composition comprising a therapeutically effective anount of a compound as defined in claims 1, 2, 3, 4 or 5 together with pharmaceutically acceptable carriers, excipients or diluents.

7. A method for treatment or prophylaxis of an animal or human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), lower perhalo

alkoxy (C_1-C_4), unsubstituted amino, N-lower alkyl (C_1-C_4) amino or N-lower alkyl (C_1-C_4) amino carbonyl;

R_1 represents a hydrogen, hydroxyhydroxymethyl, amino, alkoxy, carbamoyl or halogen (fluorine, chlorine, bromine and iodine);

R_2 represents a C_3-C_7 cycloalkyl ring in which from 1 to 4 hydrogen atoms are substituted with fluorine atoms, or sulphonamide derivatives;

W represents $(CH_2)_p$, where p represents 0 to 1;

X represents an oxygen, sulphur, nitrogen or no atom;

Y represents CHR_5CO wherein R_5 represents hydrogen or methyl or $(CH_2)q$ wherein q represents 0 to 4;

Z represents oxygen, sulphur, NR_{10}, wherein R_{10} represents hydrogen or C_{1-6} alkyl;

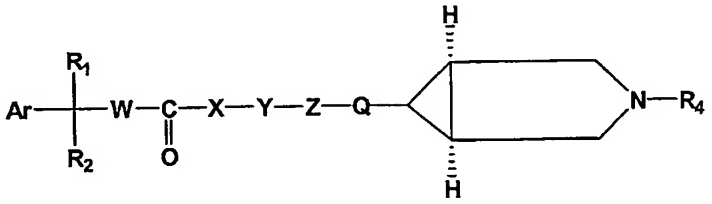
Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);

R_6 and R_7 are independently selected from H, CH_3, COOH, $CONH_2$, NH_2 or CH_2NH_2; and

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-

C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4).

8. A method for treatment or prophylaxis of an animal or human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula II



Formula II

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), lower perhalo alkoxy (C_1-C_4), unsubstituted amino, N-lower alkyl (C_1-C_4) amino or N-lower alkyl (C_1-C_4) amino carbonyl;

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (fluorine, chlorine, bromine or iodine);

R_2 represents a C_3-C_7 cycloalkyl ring in which from 1 to 4 hydrogen atoms are substituted with fluorine atoms, or sulphonamide derivatives;

W represents $(CH_2)_p$, where p represents 0 or 1;

X represents oxygen, sulphur, nitrogen or no atom;

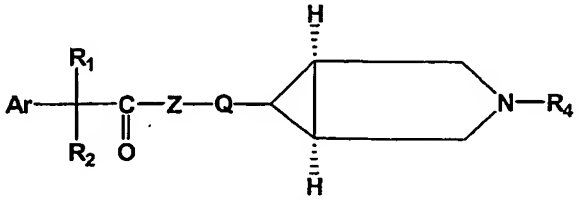
Y represents CHR_5CO wherein R_5 represents hydrogen or methyl or $(CH_2)q$ wherein q represents 0 to 4;

Z represents oxygen, sulphur or NR_{10}, wherein R_{10} represents hydrogen or C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4); and

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4).

9. A method for treatment or prophylaxis of an animal or human suffering from a disease or disorder of the respiratory, urinary, and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula III



Formula III

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, distereomers, N-oxides, polymorphs, prodrugs, metabolites wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), lower perhalo alkoxy (C_1-C_4), unsubstituted amino, N-lower alkyl (C_1-C_4) amino or N-lower alkyl (C_1-C_4) amino carbonyl;

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (fluorine, chlorine, bromine or iodine);

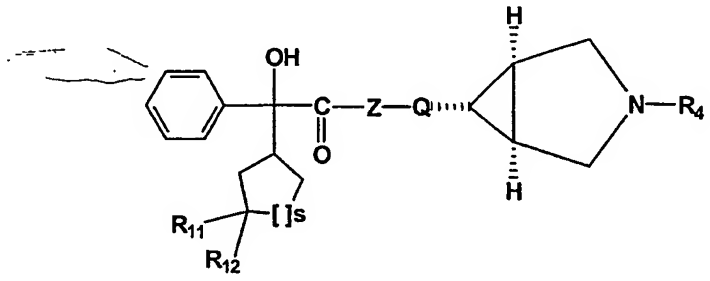
R_2 represents a C_3-C_7 cycloalkyl ring in which from 1 to 4 hydrogen atoms are substituted with fluorine atoms, or sulphonamide derivatives;

Z represents oxygen, sulphur or NR_{10}, wherein R_{10} represents hydrogen or C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4); and

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4).

10. A method for treatment or prophylaxis of an animal or human suffering from a disease or disorder of the respiratory, urinary or gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula IV



Formula IV

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, N-oxides, prodrugs or metabolites, wherein

R_{11} is hydrogen or fluoro, R_{12} is fluoro or sulphonamide derivatives and s represents 1 to 2;

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4);

Z represents oxygen, sulphur or NR_{10}, wherein R_{10} represents hydrogen or C_{1-6} alkyl; and

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4).

11. The method according to claim 7 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

12. The method according to claim 8 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes or gastrointestinal hyperkinesis.

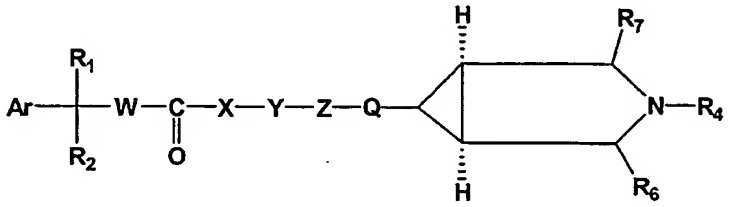
13. The method according to claim 9 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS) bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

14. The method according to claim 10 the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

15. The method for treatment or prophylaxis of an animal or human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human a therapeutically effective amount of the pharmaceutical composition according to claim 6.

16. The method according to claim 15 wherein the disease or disorder is urinary incontinence, lower urinary tract sysmptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

17. A process of preparing a compound of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxy, nitro, lower alkoxy (C_1-C_4), lower perhalo alkoxy (C_1-C_4), unsubstituted amino, N-lower alkyl (C_1-C_4) amino or N-lower alkyl (C_1-C_4) amino carbonyl;

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (fluorine, chlorine, bromine and iodine);

R_2 represents a C_3-C_7 cycloalkyl ring in which from 1 to 4 hydrogen atoms are substituted with fluorine atoms, or sulphonamide derivatives;

W represents $(CH_2)_p$, where p represents 0 to 1;

X represents an oxygen, sulphur, nitrogen or no atom;

Y represents CHR_5CO wherein R_5 represents hydrogen or methyl or $(CH_2)q$ wherein q represents 0 to 4;

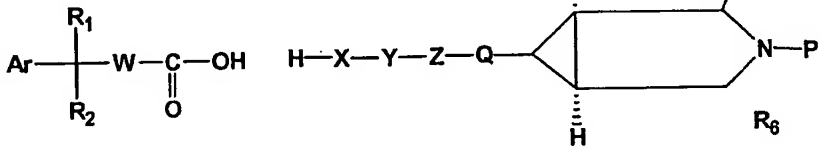
Z represents oxygen, sulphur, NR_{10}, wherein R_{10} represents hydrogen or C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);

R_6 and R_7 are independently selected from H, CH_3, COOH, $CONH_2$, NH_2 or CH_2NH_2; and

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4), comprising

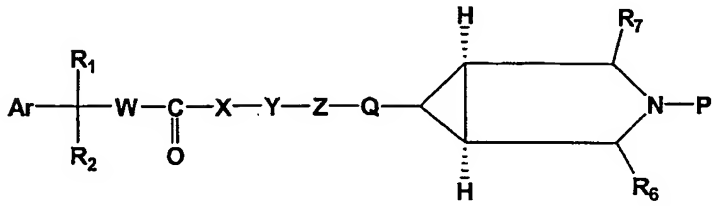
(a) condensing a compound of Formula VI with a compound of Formula V



FORMULA VI FORMULA V

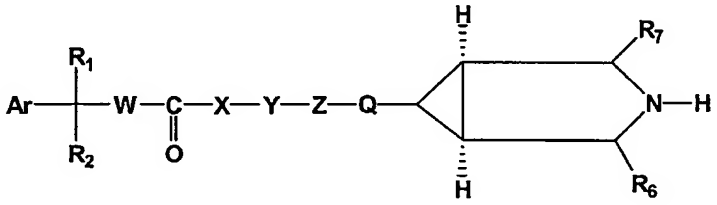
wherein Ar, R_1, R_2, W, X, Y, Z, Q, R_6 and R_7 have the same meanings as defined earlier for Formula I, to give a protected compound of Formula VII

wherein Ar, R_1, R_2, W, X, Y, Z, Q, R_6 and R_7 are the same as defined earlier and P is a protecting group for an amino group,



FORMULA VII

(b) deprotecting the compound of Formula VII in the presence of a deprotecting agent to give an unprotected intermediate of Formula VIII wherein Ar, R_1, R_2, W, X, Y, Z, Q, R_6 and R_7 are the same as defined earlier, and



FORMULA VIII

(c) the intermediate of Formula VIII is N-alkylated or benzylated with a suitable alkylating agent or benzylating agent to give a compound of Formula I.

18. The process according to claim 17 wherein P is any protecting group for an amino group and is selected from the group consisting of benzyl or t-butyloxy carbonyl groups.

19. The process according to claim 17 wherein the reaction of a compound of Formula V with a compound of Formula VI to give a compound of Formula VII is carried out in the presence of a condensing agent which is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU).

20. The process according to claim 17 wherein the reaction of a compound of Formula V with a compound of Formula VI to give a compound of Formula

VII is carried out in the presence of a suitable solvent selected from the group consisting of N,N-dimethylformamide, dimethylsulphoxide, toluene and xylene.

21. The process according to claim 17 wherein the reaction of a compound of Formula V with a compound of Formula VI is carried out at about 0-140°C.

22. The process according to claim 17 wherein the deprotection of a compound of Formula VII to give a compound of Formula VIII is carried out with a deprotecting agent which is selected from the group consisting of palladium on carbon, trifluoroacetic acid (TFA) and hydrochloric acid.

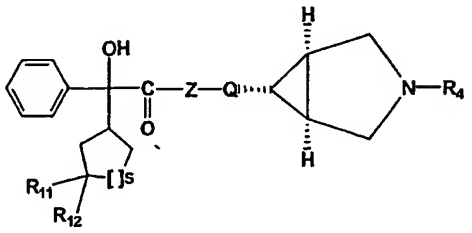
23. The process according to claim 17 wherein the deprotection of a compound of Formula VII to give a compound of Formula VIII is carried out in a suitable organic solvent selected from the group consisting of methanol, ethanol, tetrahydrofuran and acetonitrile.

24. The process according to claim 17 wherein the N-alkylation or benzylation of a compound of Formula VIII to give a compound of Formula I is carried out with a suitable alkylating or benzylating agent, L-R_4, wherein L is any leaving group and R_4 is the same as defined earlier.

25. The process according to claim 24 wherein the leaving group is selected from the group consisting of halogen, O-mestyl and O-tosyl group.

26. The process according to claim 24 wherein the N-alkylation or N-benzylation of a compound of Formula VIII to give a compound of Formula I is carried out in a suitable organic solvent selected from the group consisting of N,N-dimethylformamide, dimethylsulphoxide, tetrahydrofuran and acetonitrile.

27. A process for preparing a compound of Formula IV



FORMULA IV

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

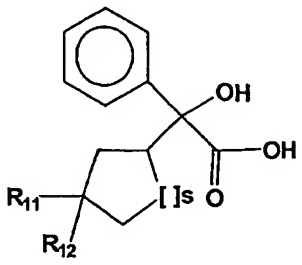
R_{11} is hydrogen or fluoro, R_{12} is fluoro or sulphonamide derivatives and s represents 1 to 2;

Z represents oxygen, sulphur, NR_{10}, wherein R_{10} represents hydrogen, C_{1-6} alkyl;

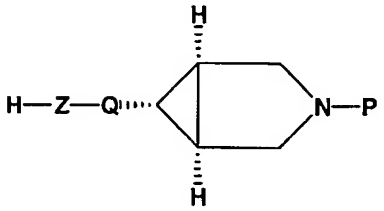
Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4); and

R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulphur atoms with option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4), N-lower alkylamino carbonyl (C_1-C_4), comprising

(a) condensing a compound of Formula IX with a compound of Formula X

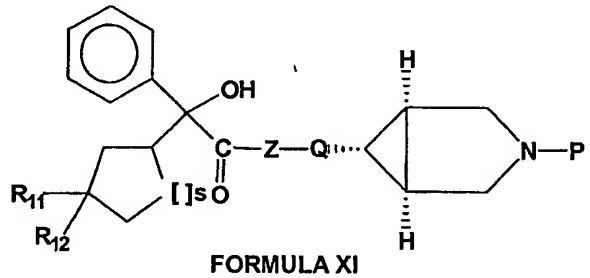


FORMULA IX



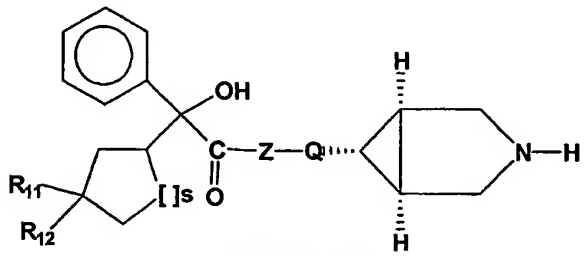
FORMULA X

where Z, Q, R_{11}, R_{12} and s have the same meanings as defined earlier for Formula IV, to give a protected compound of Formula XI,



FORMULA XI

(b) deprotecting the compound of Formula XI in the presence of a deprotecting agent to give an unprotected intermediate of Formula XII where Z, Q, R_{11}, R_{12}, s have the same meanings as defined earlier, and



FORMULA XII

(c) the intermediate of Formula XII is N-alkylated or benzylated with a suitable alkylating or benzylating agent to give a compound of Formula IV wherein Z, Q, R_{11}, R_{12}, and s are the same as defined earlier.

28. The process according to claim 27 wherein P is a protecting group for an amino group and is selected from the group consisting of benzyl or t-butoxy carbonyl groups.

29. The process according to claim 27 wherein the reaction of a compound of Formula IX with a compound of Formula X to give a compound of Formula XI is carried out in the presence of a condensing agent which is selected from the group consisting of 1-(3-dimethyl aminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU).

30. The process according to claim 27 wherein the reaction of a compound of Formula IX with a compound of Formula X to give a compound of Formula XI is carried out in the presence of a suitable solvent selected from the group consisting of N,N-dimethylformamide, dimethylsulphoxide, toluene and xylene.

31. The process according to claim 27 wherein the reaction of a compound of Formula IX with a compound of Formula X is carried out at about 0-140°C.

32. The process according to claim 27 wherein the deprotection of a compound of Formula XI to give a compound of Formula XII is carried out with a deprotecting agent which is selected from the group consisting of palladium on carbon, trifluoroacetic acid (TFA) and hydrochloric acid.

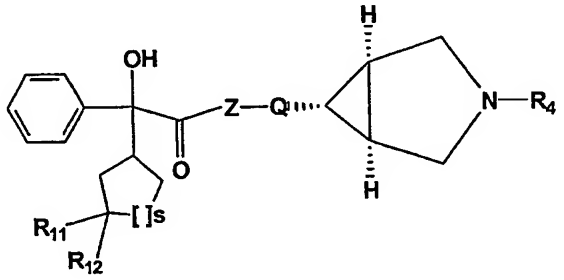
33. The process according to claim 27 wherein the deprotection of a compound of Formula XI to give a compound of Formula XII is carried out in a suitable organic solvent selected from the group consisting of methanol, ethanol, tetrahydrofuran and acetonitrile.

34. The process according to claim 27 wherein the N-alkylation or benzylation of a compound of Formula XII to give a compound of Formula IV is carried out with a suitable alkylating or benzylating agent, L-R_4, wherein L is any leaving group and R_4 is the same as defined earlier.

35. The process according to claim 34 wherein the leaving group is selected from the group consisting of halogen, O-mestyl and O-tosyl group.

36. The process according to claim 34 wherein the N-alkylation or N-benzylation of a compound of Formula XII to give a compound of Formula IV is carried out in a suitable organic solvent selected from the group consisting of N,N-dimethyl formamide, dimethylsulphoxide, tetrahydrofuran and acetonitrile.

37. A process for preparing a compound of Formula IV



FORMULA IV

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

R_{11} is H or F, R_{12} = F or substituted sulfonamide derivatives and s represents 1 to 2;

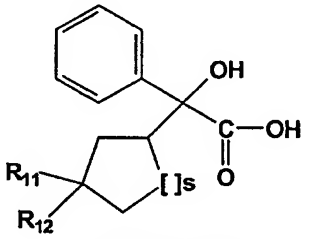
Z represents oxygen, sulphur, NR_{10}, wherein R_{10} represents hydrogen, C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4); and

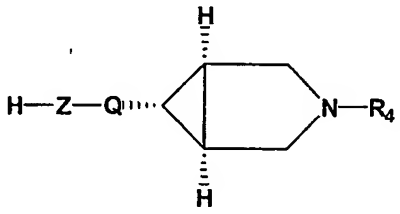
R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the

group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulphur atoms with option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4), N-lower alkylamino carbonyl (C_1-C_4), comprising

condensing a compound of Formula IX with a compound of Formula XIII



FORMULA IX



FORMULA XIII

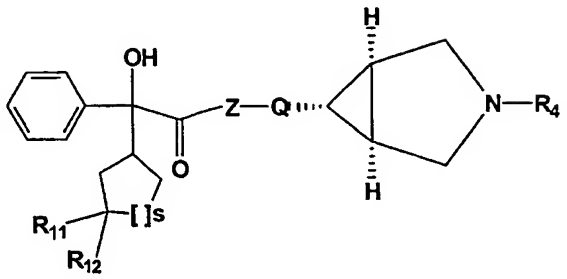
where Z, Q, R_4, s have the same meanings as defined earlier for Formula IV to give a compound of Formula IV.

38. The process according to claim 37, wherein the reaction of a compound of Formula XIII with a compound of Formula IX is carried out in the presence of a condensing agent which is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0]-undec-7-ene (DBU).

39. The process according to claim 37 wherein the reaction of a compound Formula XIII with a compound of Formula IX is carried out in the presence of a suitable solvent selected from the group consisting of N, N-dimethylformamide, dimethylsulfoxide, toluene and xylene.

40. The process according to claim 37 wherein the reaction of a compound of Formula XIII with a compound of Formula IX is carried out at about 0-140°C.

41. A process for preparing a compound of Formula IV



FORMULA IV

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

R_{11} is H or F, R_{12} = F or substituted sulfonamide derivatives and s represents 1 to 2

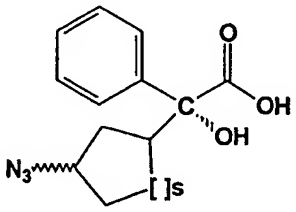
Z represents oxygen, sulphur, NR_{10}, wherein R_{10} represents hydrogen, C_{1-6} alkyl;

Q represents $(CH_2)_n$ wherein n represents 1 to 4, or CHR_8 wherein R_8 represents H, OH, C_{1-6}, alkyl, alkenyl alkoxy or CH_2CHR_9 wherein R_9 represents H, OH , lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4); and

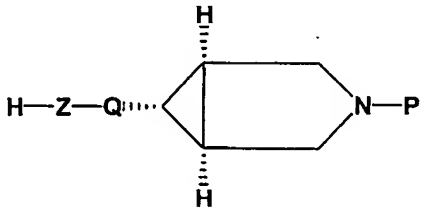
R_4 represents a C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon group in which from 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulphur atoms with option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted

amino, N-lower alkylamino (C_1-C_4), N-lower alkylamino carbonyl (C_1-C_4), comprising

(a) condensing a compound of Formula XIV with a compound of Formula X

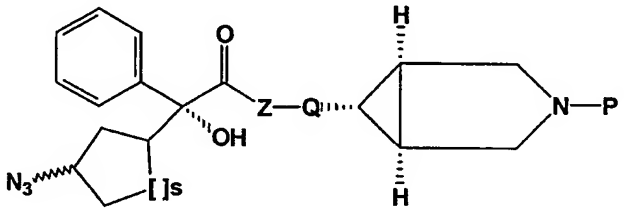


Formula XIV



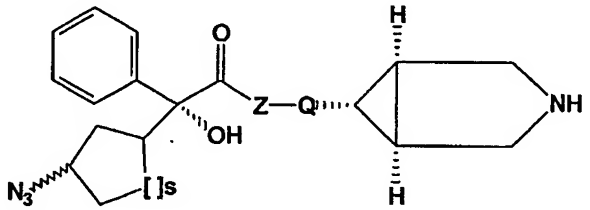
Formula X

where Z, Q, s have the same meanings as defined earlier for Formula IV, to give a protected compound of Formula XV,



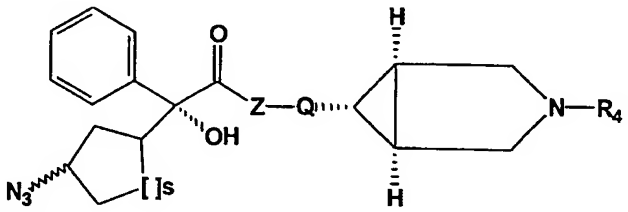
Formula XV

(b) deprotecting the compound of Formula XV in the presence of a deprotecting agent to give an unprotected intermediate of Formula XVI where Z, Q, s have the same meanings as defined earlier,



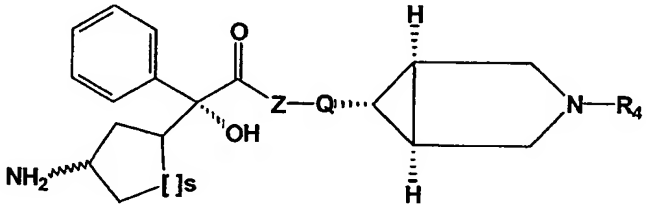
Formula XVI

(c) the intermediate of Formula XVI is N-alkylated or benzylated with a suitable alkylating or benzylating agent to give a compound of Formula XVI wherein Z, Q, R_4, s are the same as defined earlier,



Formula XVII

(d) the reduction of a compound of Formula XVII to give a compound of Formula XVII wherein Z, Q, R_4, s have the same meanings as defined earlier, and



Formula XVIII

(e) the reaction of a compound of Formula XVIII with acid chlorides to give a compound of Formula IV (R_{11}=H, R_{12}= substituted sulfonamide)

42. The process according to claim 41, wherein P is a protecting group for an amino group and is selected from the group consisting of benzyl or t-butoxy carbonyl groups.

43. The process according to claim 41 wherein the reaction of a compound of Formula XIV with a compound of Formula X to give a compound of Formula XV is carried out in the presence of a condensing agent which is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0]-undec-7-ene (DBU).

44. The process according to claim 41 wherein the reaction of a compound of Formula XIV with a compound of Formula X to give a compound of Formula XV is carried out in the presence of a suitable solvent selected from the group consisting of N,N-dimethylformamide, dimethylsulphoxide, toluene and xylene.

45. The process according to claim 41 wherein the reaction of a compound of Formula XIV with a compound of Formula X is carried out at about 0-140°C

46. The process according to claim 41 wherein the deprotection of a compound of Formula XV to give a compound of Formula XVI is carried out with a suitable deprotecting agent which is selected from the group consisting of palladium on carbon, trifluoroacetic acid (TFA) and hydrochloric acid.

47. The process according to claim 41 wherein the deprotection of a compound of Formula XV to give a compound of Formula XVI is carried out in a suitable organic solvent selected from the group consisting of methanol, ethanol, tetrahydrofuran and acetonitrile.

48. The process according to claim 41 wherein the N-alkylation or benzylation of a compound of Formula XVI to give a compound of Formula XVII is carried out with a suitable alkylating or benzylating agent, L-R_4, wherein L is any leaving group and R_4 is the same as defined earlier.

49. The process according to claim 48 wherein the leaving group is selected from the group consisting of halogen, O-mestyl and O-tosyl group.

50. The process according to claim 48 wherein the N-alkylation or N-benzylation of a compound of Formula XVI to give a compound of Formula XVII is carried out in a suitable organic solvent selected from the group consisting of N,N-dimethyl formamide, dimethylsulphoxide, tetrahydrofuran and acetonitrile.

51. The process according to claim 41 wherein the reduction of a compound of Formula XVII to give a compound of Formula XVIII is carried out in the presence of a suitable solvent selected from the consisting of tetrahydrofuran and water.

52. The process according to claim 51 wherein the reduction of a compound of Formula XVII is carried out with triphenylphosphine.

53. The process according to claim 41 wherein the reaction of a compound of Formula XVIII with acid chlorides is carried out in the presence of a suitable solvent selected from the group consisting of dichloromethane, dichloroethane and chloroform.

54. The process according to claim 53 wherein the acid chloride is selected from the group consisting of phenylacetyl chloride, 4-nitrophenylsulfonyl chloride, benzene sulfonyl chloride, benzyloxyacetyl chloride, 4-methoxyphenylsulfonyl chloride and 4-bromophenylsulfonyl chloride.

INTERNATIONAL SEARCH REPORT

PCT/IB 02/03433

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/52 A61K31/40 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	L. JEPPESEN ET AL.: "1-(1,2,5-Thiadiazol-4-yl)-4-azatricyclo‘2 .2.1.0(2.6)!heptanes as New Potent Muscarinic M1 Agonists: Structure-Activity Relationship for 3-Aryl-2-propyn-1-yloxy and 3-Aryl-2-propin-1-ylthio Derivatives" J. MED. CHEM., vol. 42, no. 11, 1999, pages 1999-2006, XP002218716 table 1 ---	1-54
A	WO 97 36906 A (NOVO NORDISK A/S) 9 October 1997 (1997-10-09) claims 1-25 ---	1-54
A	WO 95 15312 A (BASF AG) 8 June 1995 (1995-06-08) page 5, line 25; claims 1,2 ---	1-54

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 October 2002	15/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 95 15327 A (BASF AG) 8 June 1995 (1995-06-08) page 5, line 2; claims 1,2	1-54
A	US 5 397 800 A (D. ALKER ET AL.) 14 March 1995 (1995-03-14) column 1, line 6 - line 9; claims 1-6	1-54

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